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The Synthesis and Properties of the Possible Isomeric Mono-Chloro-mono-Iodo-Toluenes.

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THE introduction of iodine, using nitric acid as an oxidizing agent, was first recorded by Dyer and Mixter (*2*), who dissolved oxanilide in acetic acid and then added iodine and nitric acid. La Datta and Chatterjee (*3*), extended this method to the aromatic hydrocarbons, describing the synthesis of a number of iodo derivatives of benzene, toluene, cymene, etc.

The authors have investigated the direct iodination of the three chlorotoluenes in order to determine the proper conditions for such iodination and also to ascertain the orienting and other effects of the methyl and chlorine groups. For the sake of identification and comparison it was found necessary also to prepare nine of the ten possible isomeric chloro-iodo-toluenes, and the following paper contains a description of their synthesis and in tabular form their physical constants. While five isomers had been previously listed in the literature, four of these were again synthesized, using frequently different methods, in order to obtain additional needed data.

1. Constructed from a thesis submitted in partial fulfillment for the requirements of the degree of doctor of philosophy at the University of Kansas.
2. Dyer and Mixter: Am. Chem. J., 8, 352 (1886).
3. Basik La Datta and Nihar Rangan Chatterjee: J. Am. Chem. Soc., 39, 435 (1917)

EXPERIMENTAL.

DERIVATION OF O-CHLOROTOLUENE.

I.—1-METHYL-2-CHLORO-3-IODOTOLUENE, $CH_3C_6H_3Cl$ I.

This has been obtained in an interesting way by heating toluene m-iodo-dichloride, $CH_3C_6H_4ICl_2$ (*4*), though Wynn and Greeves (*5*) first prepared it by the method used below.

PREPARTION OF 3-NITRO-O-TOLUIDINE $CH_3C_6H_3NO_2NH_2$ (*6*).

The best yield (29 per cent) resulted when o-acet-toluide (60 gms.) was added to a mixture of fuming nitric acid (255 cc.) and glacial acetic acid (115 cc.) at 0°. After standing for three hours, the mixture was poured on ice, filtered, washed and dried. It was then saponified with sodium hydroxide (20 gms.) in alcoholic solution. After distilling off the alcohol, the residue was distilled with steam from acid solution. The slightly basic 3-nitro compound is slowly volatile with steam, while the 5-nitrotoluidine remains in the acid solution.

The amino group at position 2 was now replaced with chlorine (Sandmeyer) and the resulting 2-chloro-3-nitrotoluene reduced with tin and hydrochloric acid to the amine (yield 82 per cent), which was then diazotized in potassium iodide solution (yield 82 per cent).

The 2-chloro-3-iodotoluene thus obtained is a light yellow oil volatile with steam. When treated with fuming nitric acid it gave a nitro compound which melted at 118°.

II.—1-METHYL-2-CHLORO-4-IODOBENZENE.

The steps in the synthesis involved the nitration of p-toluidine, yielding the 2-nitro-p-toluidine (*7*), from which was obtained in good yield the 2-nitro-4-iodotoluene. (*8*.)

While the nitro group can be reduced with tin and hydrochloric acid, ferrous sulphate and ammonia gave more satisfactory results (72 per cent yield of the amine). The 1-methyl-2-amino-4-iodobenzene is volatile with steam and melts at 50° (*9*).

The hydrogen chloride salt decomposed at 240-5°.

Analyses: Calcd. for $C_7H_6IN.HCl$: HCl, 13.54. Found: 13.74.

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4. Caldwell and Werner: J. Chem. Soc., 91, 249 (1907).
5. C. B.: 1895 (2), 529.
6. Reverdin and Crepieux: Ber., 33, 2498 (1900).
7. Nolting and Collin: Ber., 17, 263 (1884).
8. Heynemann: Ann., 158, 337 (1871). Reverdin: Ber., 30, 3001 (1897).
9. Heynemann: Ann., 158, 338 (1871).

The acetyl derivative had a melting point of 183°, the benzoyl of 173°, and the picrate of 121°. The base combines with phenyl mustard oil, forming the corresponding thiourea (m.p. 152-3°). The thiourea from o-tolyl isothiocyanate melted at 162°.

The amine when diazotised with cuprous chloride gave the 2-chloro-4-iodotoluene, a light yellow oil volatile with steam. Its nitro derivative melted at 90°.

III.—1-METHYL-2-CHLORO-5-IODOBENZENE.

Wroblewski first prepared this compound from 5-amino-2-chlorotoluene (*10*), which was formed by the reduction of the nitro compound obtained by the direct nitration of o-chlorotoluene. It was synthesized here using three methods, each different from the above, and the identity of the products was proven by the fact that each with fuming nitric acid gave the same nitro derivative, melting at 84°.

Analyses: Calcd. for $C_7H_5ClINO_2$: N, 4.60. Found: 4.64, 4.51.

PREPARATION OF THE CHLOROTOLUIDINE.

METHOD A. m-Acettoluide was chlorinated with sodium chlorate and hydrochloric acid (*11*) in glacial acetic-acid solution and the resulting product hydrolyzed with boiling hydrochloric acid. The free 5-amino-2-chlorotoluene is volatile with steam and melts at 83°. The amino group was then replaced with iodine (Sandmeyer), yielding the halogen compound.

METHOD B. 2-Amino-5-iodotoluene was prepared in good yield by the direct iodination of o-toluidine in the presence of calcium or magnesium carbonate (*12*). This was then diazotised in the usual manner, replacing the amino group by chlorine.

METHOD C. The direct iodination of o-chlorotoluene. o-Chlorotoluene (45 gms.), iodine (45 gms.) and pyridine (5 cc.) were mixed and heated in a flask with ground-in condenser in a metal bath at 190-200°. In the course of an hour concentrated nitric acid (45 cc.) was added in small portions. The heating was continued for six hours until most of the iodine had disappeared, a little nitric acid being added from time to time. On cooling, the acid mixture was separated as completely as possible, the residue in the flask made alkaline and distilled with steam. The oil was purified by vacuum dis-

10. Wroblewski: Ann., 168, 211 (1873). Goldschmidt and Honig: Ber., 19, 2443 (1886); 20, 2000 (1887).

11. Reverdin and Crepieux: Ber., 33, 2503 (1900).

12. Wheeler and Liddle: Am. Chem. J., 42, 501 (1909). Artmann: Monats, 26, 1097 (1905).

tillation and the product then melted at 20°. This proved to be identical with the 5-iodo-2-chlorotoluene previously synthesized, and showed that most of the iodine had entered the ring in the position para to the chlorine. The best yield was 59 per cent. A small amount of an oily chloro-iodotoluene is also produced, which would seem to be the 3-iodo derivative.

FORMATION OF HALOGEN SUBSTITUTED BENZOIC ACIDS.

At the temperatures involved, the nitric acid oxidizes a portion of the substituted toluene to the corresponding benzoic acid. This is shown by some work of Donald M. Hetler in this laboratory, who iodinated the o-chlorotoluene at 205° and whose general results are in agreement with those of Mr. Long, so far as the chloro-iodotoluene is concerned. However, from the alkali-soluble residue in the flask was isolated o-chlorobenzoic acid (also found by Long) and two iodine-containing acids. One obtained in very small amount melted at about 195° and would seem to be impure 2-chloro-3-iodobenzoic acid (m.p. 210°). The other, which had a melting point of 145°, was proven to be 2-chloro-5-iodobenzoic acid, as follows: When 2-chlorobenzoic acid (*13*) was treated with iodine and nitric acid at 250°, an acid was obtained melting at 147°, after crystallization from boiling water.

Analyses: Calcd. for $C_7H_4ClIO_2$: Cl, 12.56; I, 44.92. Found: Cl, 12.50; I, 44.99.

The position of the iodine atom at 5 was shown by its identity with the acid formed from 5-nitro-2-chlorobenzoic acid, by reduction of the nitro to the amino group and replacement of that by iodine.

IV.—1-METHYL-2-CHLORO-6-IODOBENZENE.

Cohen and Miller (*14*) describe this as a colorless oil, prepared from 2-chloro-6-aminotoluene. It is the only isomer not synthesized in this investigation.

V.—1-METHYL-2-IODO-3-CHLOROBENZENE.

Following the method of Wheeler and Liddle (*15*), 2-amino-3-nitrotoluene was converted into 2-iodo-3-nitrotoluene, the best yield of which was 86 per cent (compare isomer I). This was reduced with ferrous sulfate and ammonia in alcoholic solution to the 3-

13. Ullmann: Am. Chem. J., 16, 533 (1894).
14. Cohn and Miller: J. Chem. Soc., 85, 1627 (1909).
15. Wheeler and Liddle: Am. Chem. J., 42, 451 (1909).

amino-2-iodo compound. The amine (40 gms.) was dissolved in hydrochloric acid (100 cc.) diluted with water and diazotized with sodium nitrite (20 gms.) and cuprous chloride (30 gms.) at 0°. After standing for several hours the solution was distilled with steam and the chloro-iodotoluene purified by vacuum distillation. The yield was only 35 per cent. The yellow oil darkened on standing, and on treatment with fuming nitric acid gave a yellow nitro derivative, which, when crystallized from gasoline, melted at 84°.

VI.—1-METHYL-3-CHLORO-4-IODOBENZENE.

Preparation.

METHOD I: CHLORINATION OF p-ACETTOLUIDE.

The acettoluide (90 gms.) was dissolved in a mixture of glacial acetic acid (300 cc.) and pure hydrochloric acid (140 cc.) and cooled in an ice bath. Forty grams of sodium chlorate in concentrated solution were added slowly during a period of three hours with constant stirring. After standing in an ice box for twenty hours the mixture was poured into water. The yield of 3-chloro-p-acettoluide was 65 per cent (*16*). The acetyl group is best removed by hydrolysis in acid solution. For this purpose it was heated with four times its weight of 35 per cent hydrochloric acid, or, better, with 20 per cent by volume of sulphuric acid. Low yields of the amine were found in some cases to be due to the splitting off of the amino group, which appeared as ammonia when the reaction mixture was made alkaline.

The amine gave in 76 per cent yield on diazotizing with potassium iodide the 3-chloro-4-iodotoluene.

METHOD 2.

It has been found that when the acetyl derivative of p-toluidine is nitrated, the nitro group enters the 3 position (*17*), forming the 3-nitro-p-acettoluide, which is easily hydrolyzed with alcoholic sodium hydroxide. The amino group was replaced with iodine in the usual manner (*18*). The 4-iodo-3-nitrotoluene is volatile with steam and melts at 54-6°. Reduction of the nitro group to the 4-iodo-3-aminotoluene is best carried out by means of ferrous sulphate and ammonia (*19*), and on replacement of the amino group

16. Reverdin and Crepieux: Ber. 33, 2500 (1900).
17. Cossack: Ber. 13, 1088 (1880).
18. Wheeler: Am. Chem. J, 44, 139 (1910). Willgerodt and Simonis: Ber. 39, 269 (1906).
19. Wheeler and Liddle: Am. Chem. J, 42, 445 (1910).

with chlorine (48 per cent yield) the same chloro-iodotoluene was obtained. It is a light yellow oil which on treatment with fuming nitric acid gave a nitro compound melting at 83-5°.

VII.—1-METHYL-3-CHLORO-5-IODOBENZENE.

Since the groups in the substituted benzene are in the symmetrical (1.3.5) positions, all meta to each other, it could not be formed by direct substitution. Hence the following procedure was adopted:

The starting point was para-toluidine, which was converted into 3-chloro-4-aminotoluene as described under isomer VI.

1-METHYL-4-AMINO-3-CHLORO-5-IODOBENZENE FROM THE IODINATION OF 3-CHLORO-p-TOLUIDINE.

A mixture of the amine (44 gms.), calcium carbonate (33 gms.), iodine (75 gms.), ether (80 cc.) and water (80 cc.) was heated under a reflux until the iodine vapor had practically disappeared. The reaction mixture was then treated with a little sodium thiosulphate and steam distilled. A light-colored oil, which solidified in the received, came over very slowly (18 hours distillation) in 72 per cent yield. After crystallization from dilute alcohol or acetone, in which it is very soluble, it melted at 87°.

Analyses: Calcd. for C_7H_7ClNI: N, 5.52. Found: 5.42.

The position of the entering iodine atom is indicated by the fact the chloro-iodotoluene obtained from it differs from the other nine isomers and also by analogy from the work of Wheeler and Liddle with p-toluidine (*20*). They found that when this amine was treated with two mols of iodine the 3-5-di-iodo-p-toluidine resulted.

BENZOYL DERIVATIVE OF 3-CHLORO-5-IODO-p-TOLUIDINE.

This, made by the Schotten-Baumann reaction, melted at 167° after crystallization from alcohol.

Analyses: Calcd. for $C_{14}H_{11}ClINO$: N, 3.77. Found: 3.83, 3.78.

The amine is too weak a base to form a salt when dry hydrogen chloride is passed into its benzene solution.

ELIMINATION OF THE AMINO GROUP.

The base was diazotized with solid sodium nitrite, using concentrated sulphuric acid and absolute alcohol (*20*). A 70 per cent yield of the 3-chloro-5-iodotoluene was obtained after distillation with steam. It is a light yellow oil which gave on treatment with fuming nitric acid a nitro compound melting at 101°.

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20. Wheeler: Am. Chem. J, 44, 144 (1910).

VIII.—1-METHYL-3-CHLORO-6-IODOBENZENE. (*21*)

(1-METHYL-2-IODO-5-CHLOROBENZENE.)

Preparation.

METHOD 1: FROM O-ACETTOLUIDE.

This was chlorinated in acetic acid solution with sodium chlorate and hydrochloric acid and the acetyl derivative hydrolyzed with concentrated hydrochloric acid (40 gms. substance to 300 cc. acid). The free base, 2-amino-5-chlorotoluene, was then diazotized in the presence of potassium iodide. The chloro-iodotoluene is a stable oil (60 per cent yield) volatile with steam. It gives a nitro derivative melting at 88°.

METHOD 2: ACTION OF IODINE-MONO-CHLORIDE ON META-ACETTOLUIDE.

Wheeler (*22*) has shown that the 3-amino-6-iodotoluene can be easily made by the action of iodine chloride on m-acettoluide and hydrolysis of this product with excess of sodium hydroxide. If hydrochloric acid is used in the hydrolysis iodine is liberated and no pure product can be obtained. The replacement of the amino group by chlorine (Sandmeyer) was not satisfactory, the yield being only 25 per cent.

IX.—1-METHYL-2-IODO-4-CHLOROBENZENE. (*23.*)

This compound had been previously described by Wroblewski. His general method was followed though the intermediates were isolated in a more pure state. The reduction of 2-nitro-4-chlorotoluene from p-chlorotoluene gave the 2-amino-4-chlorotoluene, melting at 21-2° (*24*). This when diazotized gave in 78 per cent yield the desired chloro-iodotoluene. This is a light orange-yellow oil volatile with steam. With fuming nitric acid a nitro product melting at 166° was obtained.

X.—1-METHYL-3-IODO-4-CHLOROBENZENE.

This was synthesized by two methods—substitution of the amino group by chlorine in 3-iodo-p-toluidine, and by the direct iodination of p-chlorotoluene.

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21. Beilstein Kuhlberg: Ann. 156, 82 (1870).
22. Wheeler: Am. Chem. J, 44, 130 (1910).
23. Wroblewski: Am. 168, 210 (1875).
24. Goldschmidt and Honig: Ber. 19, 243, 842 (1886).

METHOD 1.

Para-toluidine was treated with iodine and calcium carbonate according to the method of Wheeler and Liddle (*25*), giving the 3-iodo-4-aminotoluene. The mono-iodotolyl urea, $CH_3C_6H_3INHCONH_2$, melts at 192° (Wheeler, 187°). On replacing the amino group with chlorine, an oil volatile with steam was obtained which proved to be the desired chloro-iodotoluene. This reacted with fuming nitric acid at 0°, giving a nitro compound that melted at 162°.

METHOD 2: DIRECT IODINATION OF P-CHLOROTOLUENE.

Para-chlortoluene (60 gms.), iodine (60 gms.) and pyridine (5 cc.) were heated in a metal bath at 195°. To this was added in the course of an hour a mixture of concentrated nitric acid containing 25 per cent of fuming acid. The heating was continued for a number of hours, adding a little nitric acid from time to time. When the iodine has disappeared the residue in the flask was steam distilled. The oil that came over proved to be the 3-iodo-4-chlorotoluene (42 per cent yield). The last of the distillate, ten grams in all, was a solid melting at 85°, and was found by analysis to be a di-iodo compound, $C_7H_5ClI_2$.

Analyses: Calcd. for $C_7H_5ClI_2$: Cl., 9.38; I, 67.11. Found: Cl., 9.36; I, 66.98.

It has doubtless the following structure, viz.: 1-methyl-4-chloro-3-5-di-iodobenzene, since it results from the further iodination of the 4-chloro-3-iodotoluene, and experiment has shown that a second iodine enters the 5-position of 4-amino-3-iodotoluene. Further light on the reaction was obtained by Mr. Hetler, who carried out the iodination at a higher temperature, 220-25°, which increased very definitely the oxidizing action of the nitric acid.

HALOGEN ACIDS FROM THE IODINATION OF p-CHLOROTOLUENE.

From the alkali soluble portion of the residue was isolated p-chlorobenzoic acid (m. p. 235°) and a small amount of an impure acid containing both chlorine and iodine formed by the oxidation of the 4-chloro-3-iodotoluene.

4-CHLORO-3-IODOBENZOIC ACID.

This acid was obtained in a pure state by the oxidation of 4-chloro-3-iodotoluene, using the method of Ullmann (*26*). It melted at 208° after crystallization from dilute alcohol.

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25. Wheeler and Liddle, Am. Chem. J., 42, 445 (1909).
26. Uullmann, Am. Chem. J., 16, 553 (1894).

TABLE OF CONSTANTS.

	Melting point.	Boiling point.	Index ref. at 23.	SP. G. at 15.	Anal. calc. Cl and I. 64.35.	M. P. nitro deriv.
I. 1-Methyl-2-Chloro-3-Iodobenzene.	—12°	110–125° at 11.1 mm.	1.608	1.657	64.50	118°
II. 1-Methyl-2-Chloro-4-Iodobenzene.	8°	136.5–147.6° at 16 mm.	1.624		64.19 63.76	90°
III. 1-Methyl-2-Chloro-5-Iodobenzene.	20°	108–123° at 9.5 mm.	1.618	1.7857	64.38 63.72	84°
IV. 1-Methyl-2-Chloro-6-Iodobenzene.	oil.	132–133° at 25 mm.		1.844 at 20		
V. 1-Methyl-2-Iodo-3-Chlorobenzene.	—26°	130–145° at 25.5 mm.	1.608		63.78	84°
VI. 1-Methyl-3-Chloro-4-Iodobenzene.	—12°	120–125° at 10 mm.	1.618	1.8364	64.71 64.88	83–85°
VII. 1-Methyl-3-Chloro-5-Iodobenzene.	—12°	120–142° at 22 mm.	1.609	1.7682	64.75 64.76	101°
VIII. 1-Methyl-2-Iodo-5-Chlorobenzene.	—21°	110–125° at 5.5 mm.	1.616		64.52 64.62	88°
IX. 1-Methyl-2-Iodo-4-Chlorobenzene.	—25°	133.5–137.5° at 7.2 mm.	1.620	1.8358	64.50	166°
X. 1-Methyl-3-Iodo-4-Cholobenzene.	—10°	120–125° at 14.5 mm.	1.614	1.7940	64.20 64.57	162°

Analyses: Calcd. for $C_7H_4ClIO_2$: Cl, 12.56; I, 44.95. Found: Cl, 12.57; I, 44.90.

The same acid as shown by its analysis and mixed melting point was produced by heating p-chlorobenzoic acid, iodine and nitric acid at 290°. Its constitution, and as a result that of the original chloroiodobenzene, was proven by an independent method. Nitration of the p-chlorobenzoic acid gave the 3-nitro-4-chlorobenzoic acid which was then reduced to the 3-amino-4-chlorobenzoic acid (*27*). The acid formed by replacing the amino group by iodine melted at 208-9° and proved to be identical with the acids synthesized by the two other methods.

SUMMARY.

The table gives a résumé of the properties of the ten possible chloro-iodotoluenes. Numbers I, III, IV, VIII and IX have been previously noted in the literature. With the exception of IV, their preparation has been repeated by the same or usually different methods and additional data regarding them obtained. Numbers II, V, VI, VII and X have been synthesized by methods which proved their constitution, thus completing the list of the possible isomers. Two isomers have been obtained by direct iodination: No. III, 2-chloro-5-iodotoluene, from 2-chlorotoluene; and No. X, 3-iodo-4-chlorotoluene from p-chlorotoluene. The entering iodine atom occupies the position that would be expected, though the directing influence would seem to be mainly that of the chlorine atom. Any other possible isomers must be formed, if at all, in much smaller quantity.

The nitro derivatives were prepared simply as an aid in identification and differentiation. The question of the position of the nitro group must be left for later investigation.

The formation of m-iodobenzoic acid in this laboratory and of the two chloroiodobenzoic acids shows the possibility of iodinating benzoic and chlorobenzoic acids if sufficiently high temperatures are used.

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27. Hunn, J. Am. Chem. Soc., 45, 1057 (1923).